

**REMARKS**

Favorable consideration of this application is respectfully requested in view of the following remarks.

Claims 1, 7-8 and 13 are pending in the application. Claims 1, 7-8 and 13 have been rejected.

Claims 1, 7-8 and 13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lobaccaro et al., J. Med. Chem., Vol 40, pp. 2217-2227, 1997 (Lobaccaro et al.). Claims 1, 7-8 and 13 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over Napolitano et al., J. Med. Chem., Vol. 38, pp. 2774-2779, 1995 (Napolitano et al.).

Applicants traverse these rejections and respectfully submit that Lobaccaro et al. and Napolitano et al. do not make obvious claims 1, 7-8 and 13. Arguments previously made by Applicants in submitting that a *prima facie* case of obviousness had not been established are incorporated herein by reference (see Responses dated October 26, 2007 and February 20, 2007).

Further, Applicants respectfully submit that the evidence previously submitted to the USPTO (see Amendment dated July 30, 2004), the Rule 1.132 Declaration by pharmacologist, Antwan Ederveen (the Ederveen Declaration, a copy of which is attached hereto) is sufficient to overcome a *prima facie* case of obviousness.

The Ederveen Declaration provides evidence that the presently claimed compound of formula I containing a five-carbon chain at the 11 $\beta$  position possesses unexpected properties over homologs containing a four-carbon chain at the 11 $\beta$  position, in that the presently claimed compound possesses agonist activity at ER $\alpha$  and antagonist activity at ER $\beta$ , whereas the homologs possess agonist activity at both ER $\alpha$  and ER $\beta$ . In particular, the Examiner's attention is drawn to Table A, column D of the Ederveen Declaration wherein the relative efficacy at ER $\beta$ , i.e., whether the compound behaves as an agonist or antagonist at ER $\beta$ , was ascertained. As seen in column D, compound 2 (four-carbon chain) and compound 3 (five-carbon chain) only differ by one carbon in the side chain at position 11. For compound 2, a value of 1.17 was determined for the efficacy at

ER $\beta$  classifying compound 2 as an agonist. In contrast, for compound 3 a value of 0.00 was determined for the efficacy at ER $\beta$  indicating that the activity of ER $\beta$  was completely blocked, thereby classifying compound 3 as an antagonist at ER $\beta$ . Accordingly, there was a striking change in efficacy at ER $\beta$  going from compound 2 to compound 3. Similarly, a striking change in ER $\beta$  efficacy was also observed for compound 4 (four-carbon chain, 1.66 efficacy) when compared with compound 5 (five-carbon chain, 0.33 efficacy) and compound 6 (five-carbon chain, 0.00 efficacy) indicating that compound 4 behaves as an agonist at ER $\beta$  and that compounds 5 and 6 behave as antagonists at ER $\beta$ . With respect to the difference in efficacy value of 0.33 obtained with compound 5 versus the antagonist value of 0.00 obtained with compound 6, it is noted that a value of 0.00 may not have been obtained with compound 5 in view that in compound 5 the triple bond is in the middle of the chain attached at the 11 $\beta$  position whereas in compounds 4 and 6 the triple bond is at the end of the chain attached at the 11 $\beta$  position. Similarly, compound 7 (considered to possess a four-carbon chain) behaves as an agonist at ER $\beta$  (0.9 efficacy) whereas compound 8 (considered to possess a five-carbon chain, 0.00 efficacy) behaves as an antagonist at ER $\beta$ . Similarly, compound 10 (four-carbon chain, 0.57 efficacy) behaves as an agonist at ER $\beta$  whereas compound 11 (five-carbon chain, 0.00 efficacy) behaves as an antagonist at ER $\beta$ . Accordingly, Applicants resubmit that the differential properties observed between the C4 and C5 11 $\beta$ -compounds as demonstrated in Table A are unexpected and do not in any way follow the teachings of either Lobaccaro et al. or Napolitano et al.

In view of the above, withdrawal of the rejections of claims 1, 7-8 and 13 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below.

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